

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 9/14, 31/00, 38/00	A1	(11) International Publication Number: WO 00/30614 (43) International Publication Date: 2 June 2000 (02.06.00)
(21) International Application Number: PCT/SE99/02154 (22) International Filing Date: 22 November 1999 (22.11.99) (30) Priority Data: 9804000-9 23 November 1998 (23.11.98) SE (71) Applicant (for all designated States except US): AS-TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BISRAT, Mikael [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). MOSHASHEE, Saeed [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). NYQVIST, Håkan [SE/SE]; Astra Arcus AB, S-151 85 Södertälje (SE). DEMIRBÜKER, Mustafa [TR/SE]; Microdim, Högbyvägen 76, S-175 46 Järfälla (SE). (74) Agent: ASTRAZENECA AB; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: A PROCESS FOR PRODUCING PARTICLES WITH A CONVERTED AMORPHOUS AND/OR META-STABLE CRYSTALLINE REGION INTO CRYSTALLINE STATE <div data-bbox="390 1630 1657 2150" data-label="Diagram"> </div> (57) Abstract <p>The invention provides a process for crystallization of amorphous and/or meta-stable crystalline regions of preformed particles by treating the particles with a supercritical or subcritical fluid containing an anti-solvent and a solvent. The invention further provides formulations comprising particles produced according to the present process containing one or more pharmacologically active substances and one or more pharmaceutically acceptable excipients, use of said formulations in the treatment of an allergic and/or inflammatory condition of the nose or lungs and methods for treatment of such conditions.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

A PROCESS FOR PRODUCING PARTICLES WITH A CONVERTED AMORPHOUS AND/OR META-STABLE CRYSTALLINE REGION INTO CRYSTALLINE STATE

FIELD OF THE INVENTION

5 The present invention is directed to a process for converting amorphous and/or meta-stable crystalline regions of particles into a crystalline state, the resulting particles being useful e.g. for oral or nasal inhalation.

BACKGROUND OF THE INVENTION

10

The increasing production and use of fine powders in the pharmaceutical industry has highlighted the need for reliable methods for assessing their physicochemical and technical handling. Particles obtained by spray drying, freeze drying, rapid solvent quenching or from controlled precipitation will often be in an amorphous state and/or in a meta-stable crystalline form. For crystalline substances, a diminution operation, e.g. micronization, will
15 give particles with amorphous regions.

The usefulness of amorphous and/or meta-stable crystalline particles is limited due to their thermodynamic instability. For example, such particles tend to fuse in the presence of
20 moisture, thereby forming hard agglomerates which are difficult to break up. Furthermore, amorphous and/or meta-stable crystalline particles exhibit larger batch-to-batch variations as regards bulk density than do well-defined crystalline particles. This may cause problems e.g. in inhalers for treating respiratory disorders, due to lower dosing accuracy.

25 It is therefore desirable to convert the amorphous or meta-stable crystalline particles into a crystalline, and therefore, more stable state.

Methods to convert the amorphous or meta-stable crystalline particles into crystalline particles are known. Examples are disclosed in US 5,709,884 and US 5,562,923 both to
30 Astra AB of Sweden.

The known methods to convert amorphous or meta-stable crystalline particles into crystalline particles are, however, often time consuming requiring substantial space. Therefore, there is a need for a more efficient technique for producing crystalline particles with a high shelf life.

5

SUMMARY OF THE INVENTION

The object of the present invention is to provide a process for crystallization of amorphous and/or meta-stable crystalline regions of particles e.g. obtained in a preceding microniza-
10 tion stage, comprising treating the particles under supercritical or subcritical conditions with an anti-solvent and a solvent.

According to a preferred embodiment of the invention, the anti-solvent and solvent are carbon dioxide and water, respectively.

15

According to another preferred embodiment, the relative solvent saturation of the anti-solvent lies in the range of from 15% up to 50% of total solvent saturation at the prevailing pressure and temperature.

20

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a schematic representation of the experimental equipment used for performing the present process.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for converting amorphous and/or meta-stable crystalline regions of preformed particles into an essentially crystalline state, comprising

- 5 (a) placing the preformed particles in an apparatus suitable for supercritical or subcritical conditions;
- (b) treating the particles with a supercritical or subcritical fluid comprising an anti-solvent and a solvent; and
- (c) recovering the essentially crystalline particles.

10

The inventors of the present process, have surprisingly found that the amount of amorphous and/or meta-stable crystalline regions of preformed particles can be reduced considerably while essentially maintaining the size of the particles after applying the process of the invention.

15

Without being bound by any theory, it can be envisaged that the supercritical or subcritical anti-solvent is an extraordinarily efficient carrier, since under these circumstances the diffusivity becomes very high. In this way, the solvent molecules penetrate quickly and deeply into the amorphous and/or meta-stable crystalline regions of the preformed

20 particles.

The present process therefore, can be applied directly following a procedure where amorphous and/or meta-stable crystalline particles are produced, e.g. in a micronizing, spray-drying or freeze-drying operation.

25

In the present invention, preformed particles are conditioned without being dissolved in a solvent. Instead, the amorphous and/or meta-stable crystalline regions of the particles are directly transferred into the crystalline state by the influence of the supercritical or subcritical fluid containing an anti-solvent and a solvent.

30

A "supercritical fluid" is a fluid at or above its critical pressure (P_c) and critical temperature (T_c) simultaneously. Supercritical fluids also encompass "near supercritical fluids", which are above but close to its critical pressure (P_c) and critical temperature (T_c) simultaneously. A "subcritical fluid" is above its critical pressure (P_c) and close to its critical temperature (T_c).

The anti-solvent should be selected such that the particle substance at issue is essentially insoluble in the anti-solvent. In this way, the loss of particle substance will be minimized during the present process.

The anti-solvent is suitably one or more of carbon dioxide, nitrous oxide, sulfur hexafluoride, ethane, ethylene, propane, n-pentane, xenon, trifluoromethane, chlorotrifluoromethane, a fluorocarbon compound, a chlorofluorocarbon compound, nitrogen or water. The anti-solvent is preferably carbon dioxide.

In the present invention, the anti-solvent contains a solvent, wherein said solvent is miscible with said anti-solvent. The solvent may be a lower alkyl alcohol, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, sec-butanol or tert-butanol, an aldehyde, a ketone, an ester, a base such as ammonia or pyridine, or any mixture of any of these, as long as the mixture of anti-solvent and solvent is in one and only one phase when contacted with the particles. The solvent is suitably a polar solvent, preferably water.

Immediately before treating the particles in the conditioning vessel, the relative solvent saturation of the anti-solvent may be in the range of from about 1% up to 100%, i.e. total, solvent saturation at the prevailing pressure and temperature. Immediately before treating the particles in the conditioning vessel, the relative solvent saturation of the anti-solvent is suitably in the range of from 15% up to 50%, preferably from 20% up to 45%, and more preferably from 25% up to 40% of total solvent saturation at the prevailing pressure and temperature.

A particularly preferred combination of anti-solvent and solvent is carbon dioxide and water, advantageously when the relative water-saturated supercritical carbon dioxide (RWSSC) lies in the range from about 20% up to about 40%, and especially when the RWSSC lies in the range from 25% up to 35% of total solvent saturation at the prevailing
5 pressure and temperature..

A suitable relative solvent saturation may be obtained by pumping dry and totally solvent-saturated anti-solvent at suitable flow rates through a tee-piece such that they are completely mixed before reaching the conditioning vessel containing the particles with amorphous
10 and/or meta-stable crystalline regions. When the pressure and temperature of the dry and totally solvent-saturated anti-solvent are identical, the flow-rate ratio determines the resulting relative solvent saturation.

The flow-rate ratio between dry and totally solvent saturated anti-solvent may be in the
15 range of from about 10:1 to about 1:10, suitably from 8:1 to 1:5, preferably from 6:1 to 1:1, when preparing a supercritical or subcritical fluid which is not totally solvent saturated.

The essentially crystalline, preferably totally crystalline, particles produced according to the present process, may be subsequently treated with a dry anti-solvent in a supercritical
20 or subcritical state for avoiding precipitation of the solvent upon pressure reduction and for obtaining particularly dry particles. Preferably, the anti-solvent containing a solvent and the dry anti-solvent are both carbon dioxide.

The particles of the invention may contain one or more pharmacologically active sub-
25 stance(s) and/or one or more pharmaceutically acceptable excipients, both intended for use in mammals, preferably human beings.

Pharmaceutically acceptable excipients are e.g. carriers, additives and diluents, including antioxidants. Suitable pharmaceutically acceptable excipients include, without limitation,
30 one or more natural or synthetic carbohydrates, such as monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides and polyols, and/or in the form of their

pharmaceutically acceptable esters, acetals, salts or solvates thereof (where such derivatives exist). When the carbohydrate is in a solvated form it is suitably a hydrate, such as a monohydrate, dihydrate or trihydrate. Examples of naturally occurring monosaccharides include glucose, fructose and galactose. Examples of naturally occurring disaccharides include sucrose (saccharose), trehalose, maltose, cellobiose and lactose. The disaccharide is preferably lactose, more preferably lactose monohydrate. Examples of naturally occurring trisaccharides include raffinose and melezitose. The polysaccharide may be cellulose, starch, dextrans or dextran, or chemical derivatives of any of these. The cellulose derivative is suitably a cellulose ether such as ethylcellulose (EC), ethylmethylcellulose (EMC), hydroxyethylcellulose (HEC), ethylhydroxymethylcellulose (EHMC), ethylhydroxyethylcellulose (EHEC), methylcellulose (MC), hydroxymethylcellulose (HMC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) and carboxymethylcellulose (CMC), e.g. the sodium salt thereof. The polyol is preferably a sugar alcohol, which can be obtained by reducing various monosaccharides. For example, sorbitol and mannitol may be obtained by reducing glucose and mannose, respectively.

Pharmacologically active substances for use in the present invention can be selected from the group consisting of β agonists, including short acting and long acting β 1 and β 2 agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, and proteins and peptides, especially inhalable proteins and peptides, and any mixture thereof.

β agonists for use in the present invention include, without limitation, formoterol, salbutamol, rimiterol, fenoterol, reproterol, pirbuterol, bitolterol, salmeterol, clenbuterol, procaterol, broxaterol, picumeterol, mabuterol, terbutaline, isoprenaline, orciprenaline, adrenaline, and pharmaceutically acceptable esters, acetals, salts and solvates thereof, solvates of any of these (where such derivatives exist), and any mixture thereof.

The glucocorticosteroid, if used in the invention, is preferably an anti-inflammatory glucocorticosteroid, e.g. for use in nasal or oral inhalation, or for use in the treatment of intestinal diseases such as inflammatory bowel diseases (IBD), Crohn's disease or ulcerative

colitis. Examples of glucocorticosteroids which may be used in the present invention include betamethasone, fluticasone (e.g. as propionate), budesonide, tipredane, dexamethasone, beclomethasone (e.g. as dipropionate), prednisolone, fluocinolone (e.g. as acetonide), triamcinolone (e.g. as acetonide), mometasone (e.g. as furoate), rofleponide, flumethasone, flunisolide, ciclesonide, deflazacort, cortivazol, 16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione; 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -butylidenedioxy-17 β -methylthio-androsta-4-ene-3-one; 16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β -hydroxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-methyl ester; methyl 9 α -chloro-6 α -fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 α -carboxylate; 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydrofuran-3-yl) ester; optionally in their pure isomeric forms (where such forms exist) and/or in the form of their pharmaceutically acceptable esters, acetals or salts, where applicable, and solvates thereof. Suitably, use is made of mometasone furoate, beclomethasone dipropionate or fluticasone propionate or glucocorticosteroids with an asymmetric acetal structure, e.g. comprising 16 α ,17 α -butylidenedioxy group, such as budesonide or rofleponide as solvates where such exist.

The preformed particles of the present invention may contain pharmacologically active substance or substances premixed with one or more pharmaceutically acceptable excipients before the process of the invention is applied. This is especially advantageous if the active substance is highly potent or if the active substance is formulated with an external layer of excipients for controlled release. It is, however, also possible to prepare crystalline particles containing an active substance according to the present invention and mix them with suitable excipient(s) afterwards. In this case, the excipient particles may also be produced according to the present invention, or may be produced by some other suitable technique. It is further possible to prepare crystalline particles containing one or more excipient(s) according to the present invention and mix them with particles containing one or more active substances afterwards. In this case, the particles containing an active substance may

also be produced according to the present invention, or may be produced by some other suitable technique.

The degree of crystallinity can be measured using various analytical techniques. Isothermal microcalorimetry is a sensitive analytical technique which can be used advantageously as a measure of crystallinity. The technique determines the energy content of the particles by measuring the heat given off by amorphous and/or meta-stable crystalline regions during crystallization when the particles are subjected to a solvent-containing, normally water-containing, atmosphere. The TAM value is obtained using a Thermal Activity Monitor 2277 apparatus (Thermometrics AB, Sweden). Reference is made to Buckton, G. and Darcy, P., Int. J. Pharmaceutics, 123 (1995), pp. 265-271 and US 5,709,884 to Astra AB, especially col. 5-6.

With the present process, it is possible to drastically reduce the energy content of the particles and therefore also the TAM value. Thus, the TAM value for the particles measured before and after the conditioning step may be reduced by a factor of more than 5, suitably more than 10, more suitably more than 10^2 , and preferably by a factor of more than 10^3 .

More particularly, with the present process it is possible to produce and recover essentially crystalline compounds according to the invention with a TAM value of less than about 3 J/g, suitably less than 1 J/g, and preferably less than 0.5 J/g. One typical example is lactose monohydrate giving a TAM value of 0.1 – 1 J/g (see Example, Table 3).

Generally, the particles produced may have a particle size of less than about 500 μm , suitably less than 200 μm , and preferably with an MMD in the range of from 1 to 80 μm .

When the particles produced contain a pharmacologically active substance the particles are suitably in a finely divided form, preferably having a mass median diameter (MMD) (as measured using a Coulter counter) of less than about 20 μm , more preferably of less than

10 μm , and most preferably with an MMD in the range of from 1 to 6 μm . The particles may alternatively be in an ultra fine form, e.g. having an MMD of less than 1.0 μm .

When the particles produced contain one or more pharmaceutically acceptable excipients
5 the particles may have a mass median diameter (MMD) (as measured using a Coulter counter) of less than about 100 μm , suitably of less than 50 μm , preferably with an MMD of less than 20 μm , and more preferably with an MMD of less than 10 μm .

Finely divided particles, i.e. essentially particles having an MMD of less than about 10 μm ,
10 may be produced by conventional techniques known *per se*, e.g. by micronization or by direct precipitation. Information about micronization can be found e.g. in "The Theory and Practice of Industrial Pharmacy", Lachman, Liebermann and Klang, 2nd Ed., 1976, Lea & Febiger, Philadelphia, USA.

15 The present process is carried out under supercritical or subcritical conditions. The precise conditions of operation are dependent e.g. upon the choice of anti-solvent. It is, however, desirable that the combination of pressure and temperature is selected such that the particles essentially maintain their chemical purity and physical form after the conditioning step. Table 1, lists the critical pressure (P_c) and critical temperature (T_c) for some anti-solvents.

20

TABLE 1

Anti-solvent	P_c (bar)	T_c ($^{\circ}\text{C}$)
Carbon dioxide	74	31
Nitrous oxide	72	36
Sulfur hexafluoride	37	45
Ethane	48	32
Ethylene	51	10
Xenon	58	16

Trifluoromethane	47	26
Chlorotrifluoromethane	39	29

In practice, it may be preferable to maintain the pressure inside the conditioning vessel substantially above the relevant P_c whilst the temperature is only slightly above the T_c . Generally, therefore, the pressure may be in the range of from about 10 up to about 300 bar higher than the relevant P_c , suitably in the range of from 20 up to 200 bar higher, and preferably be in the range of from 30 up to 100 bar higher than the relevant P_c . Generally, also, the temperature may be in the range of from about 5 up to about 50°C above the relevant T_c , suitably in the range of from 10 up to 40°C above, and preferably in the range of from 15 up to 30°C above the relevant T_c .

With carbon dioxide, the pressure may be in the range of from about 80 up to about 400 bar, suitably in the range of from 100 to 250 bar, preferably in the range of from 110 to 150 bar whilst the temperature may be in the range of from about 35 up to about 80°C, suitably in the range of from 40 up to 70°C, preferably in the range of from 45 up to 60°C.

The supercritical or subcritical fluid containing an anti-solvent and a solvent should be pumped through the conditioning vessel for a period of time selected such that the desired particle characteristics are obtained. The period of time can be regulated by altering the pressure, temperature and/or flow rate. The supercritical or subcritical fluid containing an anti-solvent and a solvent can be pumped for a period of time in the range of from about 5 min up to about 48 hours, suitably from 15 min up to 24 hours, preferably from 30 min up to 12 hours.

Conveniently, the present process is carried out as a one-way process, i.e. the supercritical or subcritical fluid passes the conditioning vessel only once. It is, however, possible to recirculate the supercritical or subcritical fluid after essentially restoring the initial relative or total solvent saturation value before the fluid reenters the conditioning vessel.

An apparatus suitable for use as a conditioning vessel in the present process, must be able to withstand the pressure and temperature prevailing at the preselected supercritical or subcritical condition. Furthermore, the apparatus must be able to with-stand the impact of the anti-solvent/solvent mixture at issue under supercritical or subcritical conditions.

According to the invention there is also provided a pharmaceutical formulation comprising one or more pharmacologically active substances and one or more pharmaceutically acceptable excipients at least one of which produced according to the present invention.

Examples of such excipients include carriers such as carbohydrates e.g. in a solvated form, additives such as antioxidants, and diluents. The active substance(s) are preferably selected from the group consisting of β agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, and any mixture thereof.

The invention further provides formulations produced according to the present process containing one or more pharmacologically active substance(s) selected from the group consisting of β agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, mixed with one or more pharmaceutically acceptable excipient(s), for use in the treatment of a respiratory disorder such as an allergic and/or inflammatory condition of the nose or lungs, e.g. chronic obstructive pulmonary disease (COPD), rhinitis or asthma, or for use in the treatment of intestinal diseases such as inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis.

The invention further provides a method for treatment of an allergic and/or inflammatory condition of the nose or lungs by administering to a mammal, especially a human being, suffering from such a condition a therapeutically effective amount of a formulation containing one or more pharmacologically active substance(s) selected from β agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, mixed with one or more pharmaceutically acceptable excipient(s). More specifically, the invention provides a method for treatment of chronic obstructive pulmonary disease (COPD),

rhinitis, asthma or other allergic and/or inflammatory conditions, or for treatment of intestinal diseases such as inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis by administering to a mammal, especially a human being, suffering from such a condition a therapeutically effective amount of a formulation containing one or more
5 pharmacologically active substance(s) selected from β agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, mixed with one or more pharmaceutically acceptable excipient(s).

The invention will be illustrated by the following example which is not intended to limit
10 the scope of the invention.

EXAMPLE

Experiments were performed according to the invention in the equipment shown in Fig. 1, wherein carbon dioxide with a relative water-saturation in the range of from 20 to 40% was
15 used for crystallizing amorphous lactose monohydrate.

A conditioning vessel (CC, Keystone SFE) with a volume of 50 ml was packed with 400-500 mg of amorphous lactose monohydrate.

20 Dry supercritical carbon dioxide was pumped through the conditioning vessel using CO₂ pump 1 until the desired pressure was reached.

Supercritical carbon dioxide totally saturated with water vapor was prepared by passing dry supercritical carbon dioxide (using a CO₂ pump 2) through a water-saturation vessel
25 (WSC, Keystone SFE) used as a water reservoir. The water-saturation vessel was filled with a bed of chemical clean filter paper and 1-3 ml of water was poured into the paper bed.

Both the water-saturation vessel (WSC) and the conditioning vessel (CC) were placed
30 vertically in the oven (shown as a square) where the temperature was controlled.

The pressure inside the water-saturation and conditioning vessels was regulated using a common back pressure regulator (R) from Jasco, Japan. Pulse dampeners (PD) were used to reduce the pressure fluctuations in the equipment.

5

Once the system reached steady state with respect to the temperature and pressure, the dry supercritical carbon dioxide was mixed with the supercritical carbon dioxide totally saturated with water vapor, i.e. carbon dioxide where the relative water-saturated supercritical carbon dioxide (RWSSC) was 0 % and 100 %, respectively. In this way, desirable
10 relative water-saturated supercritical carbon dioxide (RWSSC) was obtained for conditioning the amorphous lactose monohydrate inside the conditioning vessel.

After conditioning the lactose monohydrate sample for 2 hours, the system was depressurized. The conditioned lactose monohydrate was collected, weighed and analyzed.

15

Between the test runs, the conditioning vessel was rinsed with 1-1.5 vessel volumes of dry carbon dioxide.

TABLE 2

20 Working conditions used for conditioning of amorphous lactose monohydrate

Batch no.	Pressure (bar)	Temperature (°C)	CO ₂ flow rate ratio (dry: totally sat.)	RWSSC (%)
1	120	40	16:4	20
2	120	40	14:6	30
3	120	70	12:8	40
4	120	40	12:8	40

The physical characteristics of each sample following the treatment according to the invention are shown in Table 3. The characteristics of an untreated sample is shown for comparison (Batch No. 0).

- Dv90 is a measure of the particle size. Dv90 means that 90% of the particles have a size smaller than the size at issue.
- Dv(90-10) is a measure of the particle size distribution. Dv(90-10) is the difference between Dv90 and Dv10 (10% of the particles have a size smaller than the size at issue).

The particle size and particle size distribution for each sample was measured as the mass median diameter (MMD), Dv90 and Dv(90-10) using a Coulter counter.

TABLE 3

Characteristics of lactose monohydrate treated according to the invention

Batch No.	MMD (μm)	Dv90	Dv(90-10)	TAM (J/g)
0	2.7	-	3.5	9.4
1	2.7	4.8	3.5	1
2	2.7	4.9	3.6	0.5
3	2.7	4.9	3.6	0.4
4	5.48	17.2	-	0.1

- As is evident from Table 3, the batches treated according to the present invention (Batch No. 1-4) have a lower TAM value, i.e. higher crystallinity, than the untreated sample (Batch No. 0).

CLAIMS

1. A process for converting amorphous and/or meta-stable crystalline regions of preformed particles into an essentially crystalline state, comprising
 - 5 (a) placing the preformed particles in an apparatus suitable for supercritical or subcritical conditions;
 - (b) treating the particles with a supercritical or subcritical fluid comprising an anti-solvent and a solvent; and
 - (c) recovering the essentially crystalline particles.
- 10 2. The process according to claim 1, wherein the anti-solvent is carbon dioxide.
3. The process according to claim 1 or 2, wherein the temperature lies in the range of from about 5 up to about 50°C above the critical temperature (T_c) of the anti-solvent,
15 preferably in the range of from 15 up to 30°C above the T_c .
4. The process according to any previous claim, wherein the pressure lies in the range of from about 10 up to about 300 bar higher than the critical pressure (P_c) of the anti-solvent, preferably in the range of from 30 up to 100 bar higher than the P_c .
- 20 5. The process according to any previous claim, wherein the solvent is a polar solvent.
6. The process according to claim 5, wherein the polar solvent is water.
- 25 7. The process according to any previous claim, wherein before treating the particles the supercritical or subcritical fluid is saturated with the solvent in the range of from 15% up to 50%, preferably from 25% up to 40% of total solvent-saturation at the prevailing pressure and temperature.

8. The process according to any previous claim, wherein the particles comprise one or more pharmaceutically acceptable carbohydrates selected from the group consisting of monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides and polyols, and any esters, acetals, salts or solvates thereof.
- 5 9. The process according to claim 8, wherein the disaccharide is lactose monohydrate.
10. The process according to claim 8 or 9, wherein the particles containing a carbohydrate have a mass median diameter (MMD) of less than about 100 μm , preferably less
10 than 10 μm .
11. The process according to any of the previous claims, wherein the thermal activity monitor (TAM) value of the particles after step (c) is less than 3 J/g, suitably less than 1 J/g, preferably less than 0.5 J/g.
- 15 12. The process according to any previous claim, wherein the TAM value for the particles measured before step (a) and after step (c) is reduced by a factor of more than 5, suitably more than 10^2 .
- 20 13. The process according to claim 11, wherein the thermal activity monitor (TAM) value of the lactose monohydrate particles after step (c) is less than 1 J/g, preferably less than 0.1 J/g.
- 25 14. The process according to any one of claims 1-7, wherein the particles comprise one or more pharmacologically active substance(s) selected from the group consisting of β agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, and any mixture thereof.

15. The process according to claim 14, wherein the particles containing one or more pharmacologically active substance(s) have a mass median diameter (MMD) of less than 10 μm , preferably in the range of from 1 to 6 μm .
- 5 16. The process according to any previous claim, comprising treating the particles from step (b) with a supercritical or subcritical fluid comprising a dry anti-solvent, before recovering the essentially crystalline particles.
17. The process according to claim 16, wherein the dry anti-solvent is carbon dioxide.
- 10 18. A pharmaceutical formulation comprising one or more pharmacologically active substances and one or more pharmaceutically acceptable excipients at least one of which produced according to any one of claims 1-17.
- 15 19. The pharmaceutical formulation according to claim 18, wherein the pharmacologically active substance(s) are selected from the group consisting of β agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, and any mixture thereof.
- 20 20. The pharmaceutical formulation according to claim 18 or 19, wherein the β agonist is selected from the group consisting of formoterol, salbutamol, rimiterol, fenoterol, reproterol, pirbuterol, bitolterol, salmeterol, clenbuterol, procaterol, broxaterol, picumeterol, mabuterol, terbutaline, isoprenaline, orciprenaline, adrenaline, and pharmaceutically acceptable esters, acetals, salts and solvates of any of these, and any mixture thereof.
- 25 21. The pharmaceutical formulation according to any one of claims 18-20, wherein the pharmaceutically acceptable excipient is a carbohydrate selected from the group consisting of monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides, polyols, and pharmaceutically acceptable esters, acetals, salts and solvates of any of these,
- 30 and any mixture thereof.

22. The pharmaceutical formulation according to claim 21, wherein the carbohydrate is in a solvated form, preferably as a hydrate, such as a monohydrate, dihydrate, or trihydrate.

5 23. The pharmaceutical formulation according to claim 21 or 22, wherein the carbohydrate is lactose monohydrate.

24. The pharmaceutical formulation according to any one of claims 18-23, wherein the particles have a mass median diameter (MMD) in the range of from 1 to 80 μm .

10

25. Use of the formulation according to any one of claims 18-24 in the manufacture of a medicament for use in the treatment of an allergic condition and/or inflammatory condition of the nose or lungs.

15 26. Use of the formulation according to any one of claims 18-24 in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease (COPD), rhinitis or asthma.

20 27. Use of the formulation according to any one of claims 18-24 in the manufacture of a medicament for use in the treatment of inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis.

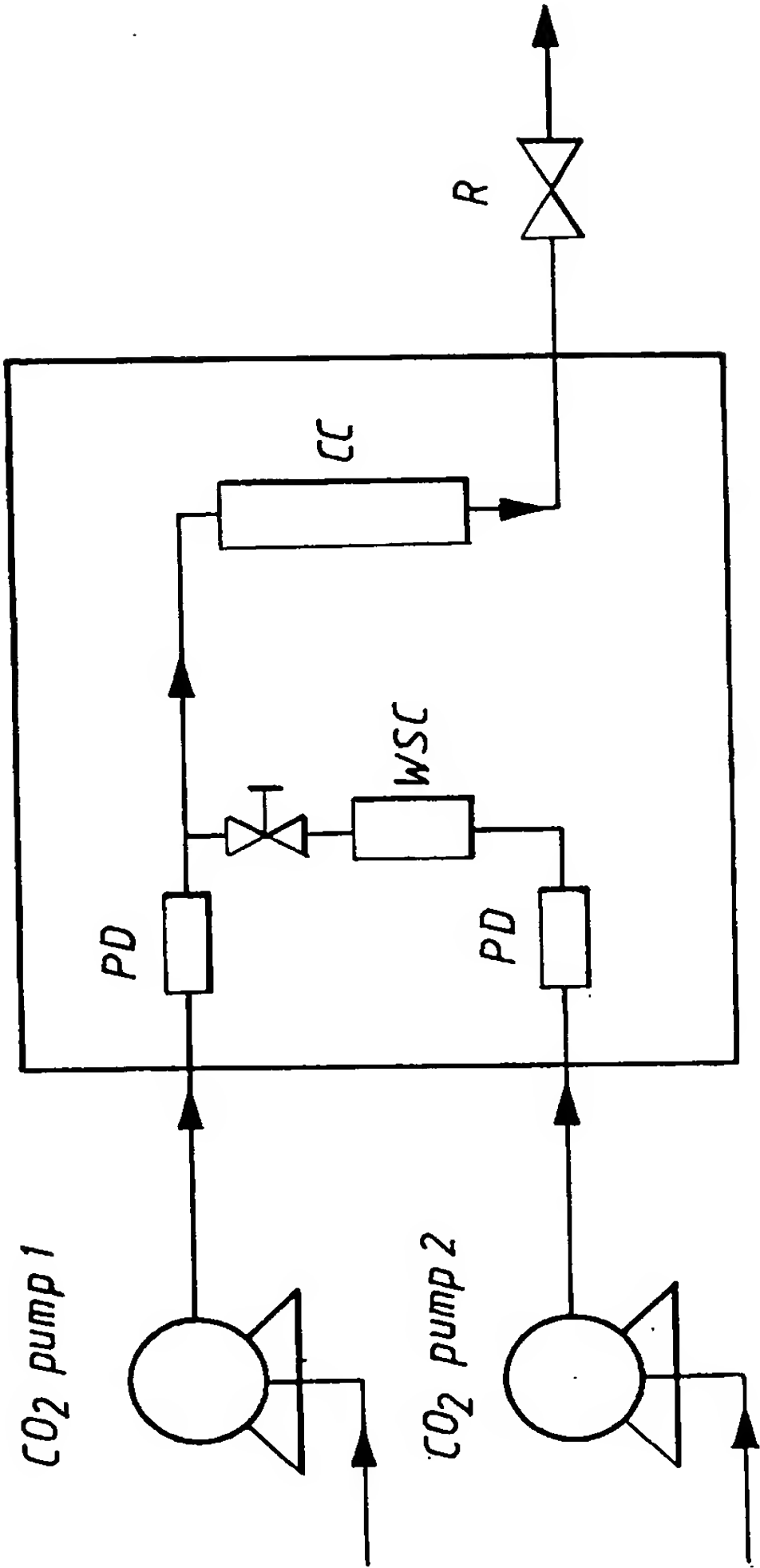
28. Method for treatment of an allergic and/or inflammatory condition of the nose or lungs comprising administering to a mammal suffering from such a condition a therapeu-
25 tically effective amount of the formulation according to any one of claims 18-24.

29. Method for treatment of chronic obstructive pulmonary disease (COPD), rhinitis or asthma comprising administering to a mammal suffering from such a condition a therapeu-
tically effective amount of the formulation according to any one of claims 18-24.

30

30. Method for treatment of inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the formulation according to any one of claims 18-24.
- 5 31. Particles of essentially crystalline state characterized by having been converted from particles with amorphous and/or meta-stable crystalline regions and having a TAM value of less than 3 J/g, suitably less than 1 J/g, preferably less than 0.5 J/g when recovered from the conversion process.
- 10 32. Lactose monohydrate particles of essentially crystalline state characterized by having been converted from particles with amorphous and/or meta-stable crystalline regions and having a TAM value of 0.1 – 1 J/g when recovered from the conversion process.

Fig. 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02154

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/14, A61K 31/00, A61K 38/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PATENT ABSTRACTS OF JAPAN, MEDLINE, EMBASE, CASEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9501221 A1 (FIDIA ADVANCED BIOPOLYMERS S.R.L.), 12 January 1995 (12.01.95), see especially page 13, line 6 - page 14, line 13; page 46, line 10 - page 47, line 29	1-26,28-29, 31-32
A	--	27,30
Y	WO 9629998 A1 (FIDIA ADVANCED BIOPOLYMERS S.R.L.), 3 October 1996 (03.10.96), page 5, line 27 - page 6, line 12; page 6, line 22 - line 25; page 7, line 19 - line 21, page 12, line 3 - line 10; page 12, line 16 - line 17; page 14, line 2 - line 11; see abstract	1-26,28-29, 31-32
A	--	27,30

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 March 2000

Date of mailing of the international search report

05 -04- 2000

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson/EÖ
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/02154

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0677332 A2 (SIEVERS, ROBERT, E.), 18 October 1995 (18.10.95), page 5, line 37 - line 42 --	6
Y	WO 9505805 A1 (ASTRA AKTIEBOLAG), 2 March 1995 (02.03.95), page 11, line 27 - page 12, line 32, abstract -- -----	11-13

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE 99/02154**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **28-30**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02154

Claims 28-30 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
PCT/SE 99/02154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501221 A1	12/01/95	AT 174530 T AU 677345 B AU 7007194 A CA 2166301 A DE 69415320 D,T EP 0706421 A,B SE 0706421 T3 ES 2128564 T GR 3029612 T JP 8511987 T NZ 267697 A SG 47392 A US 5851453 A	15/01/99 17/04/97 24/01/95 12/01/95 24/06/99 17/04/96 16/05/99 30/06/99 17/12/96 26/05/97 17/04/98 22/12/98
WO 9629998 A1	03/10/96	AU 695207 B AU 5274996 A CA 2216919 A EP 0817620 A IT 1281857 B IT PD950065 A,U,V CZ 9700808 A DE 19711957 A IT 1287194 B IT PD960021 A,U,V PL 319152 A	06/08/98 16/10/96 03/10/96 14/01/98 03/03/98 30/09/96 15/10/97 30/10/97 04/08/98 05/08/97 29/09/97
EP 0677332 A2	18/10/95	US 5639441 A	17/06/97
WO 9505805 A1	02/03/95	AU 681186 B AU 7626494 A BR 9407320 A CN 1133004 A CN 1195523 A CZ 9600544 A EP 0717616 A FI 960869 A HU 74000 A HU 9600447 D IL 110698 D JP 9501930 T NO 960744 A NZ 273090 A PL 176749 B PL 313142 A SE 9302777 D SG 47760 A SK 23496 A US 5637620 A US 5709884 A US 5874063 A ZA 9405675 A	21/08/97 21/03/95 16/04/96 09/10/96 14/10/98 15/05/96 26/06/96 26/02/96 28/10/96 00/00/00 00/00/00 25/02/97 23/02/96 24/06/97 30/07/99 10/06/96 00/00/00 17/04/98 05/02/97 10/06/97 20/01/98 23/02/99 29/04/96